Stem Cell Therapy in Diabetic Nephropathy

By

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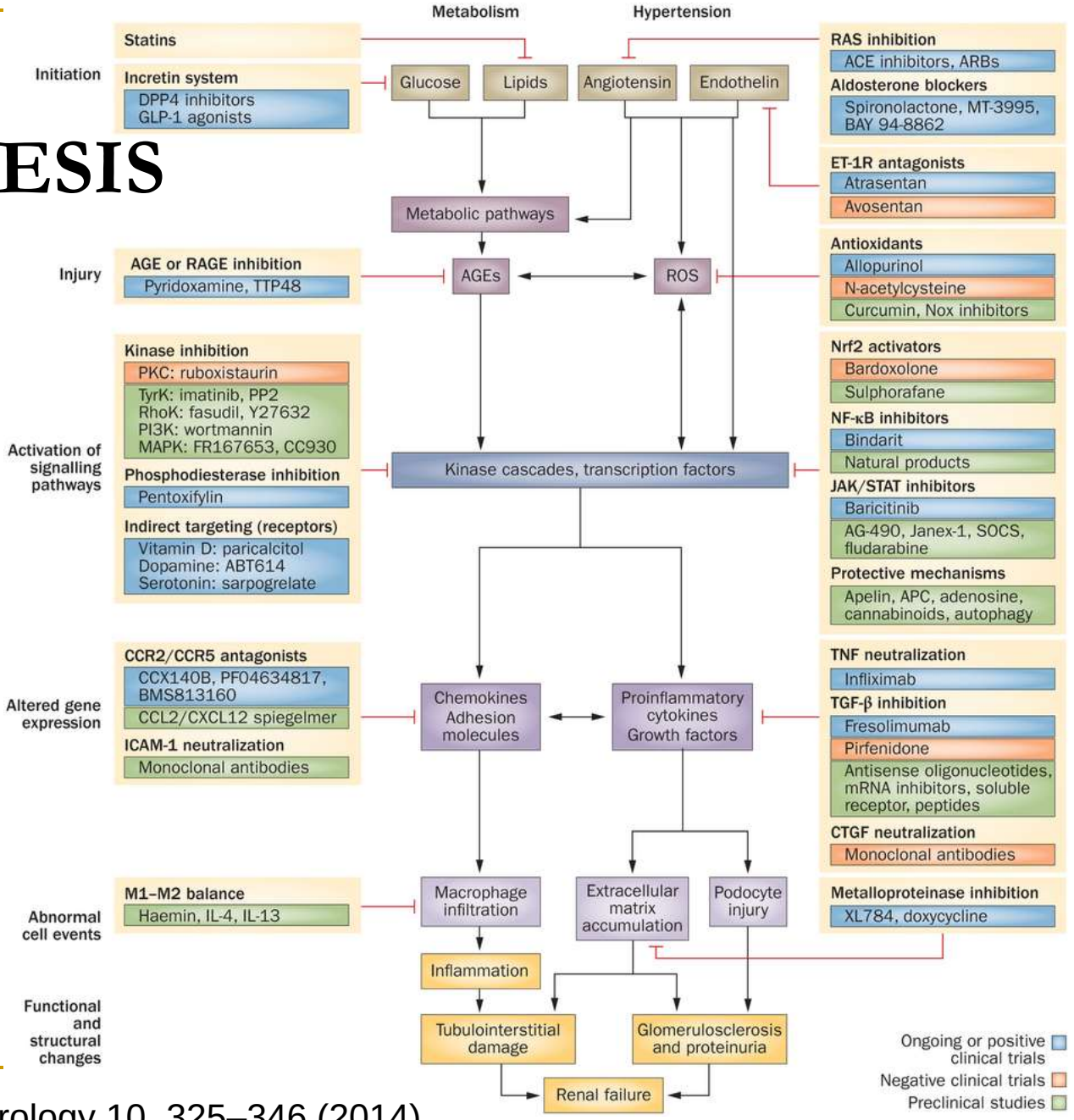
AGENDA

- Introduction
- Pathogenesis of DM
- Stem Cell types
- MSCs and DN
- Potential limitations to clinical application
- In vitro differentiation of MSCs
- Whole kidney regeneration
- conclusion

INTRODUCTION

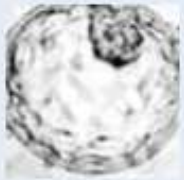
- Diabetic Nephropathy (DN) is one of the leading causes of ESRF worldwide
- Tight glycemic and hypertension control are the key factors for delaying the progression of DN
- Despite the considerable effrort to control these two factors, DN can progress even to ESRF in some patients

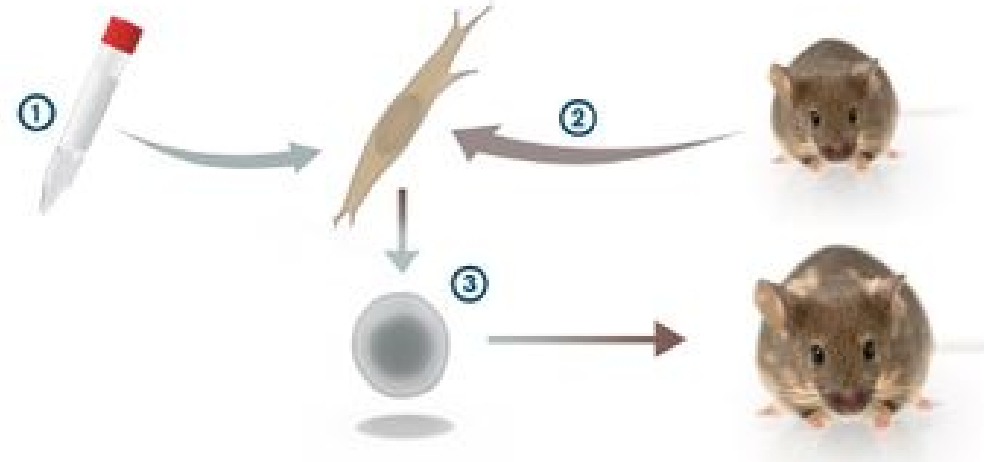
PATHOGENESIS OF DN



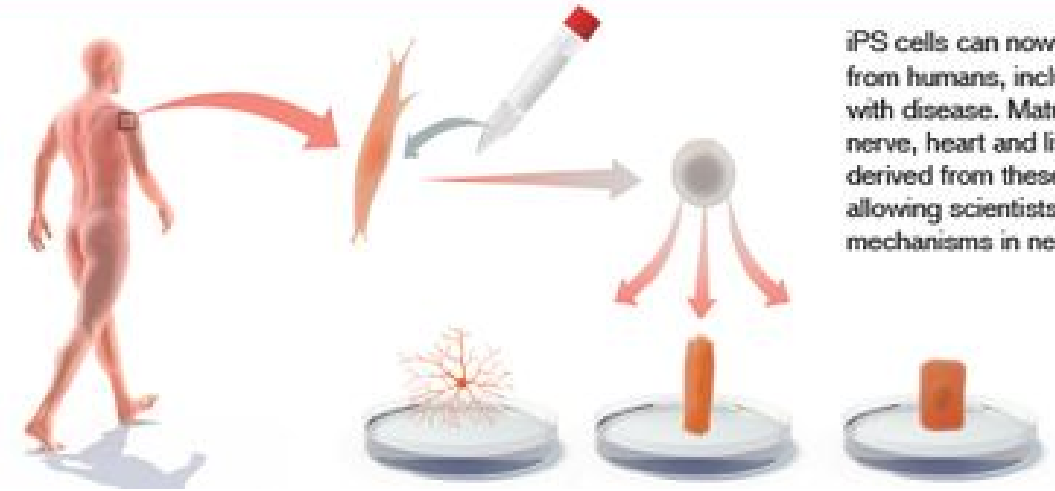
Nature Reviews Nephrology 10, 325–346 (2014)

STEM CELL TYPES

COMPARISON OF THE DIFFERENT SOURCES OF STEM CELLS			
	Embryonic Stem Cells		Adult Stem Cells
	 **In Vitro Fertilization**	 **Nuclear Transfer**	 **Adult Tissues**
Attributes	• can produce all cell types • relatively easy to identify, isolate, maintain, and grow in the laboratory • large source of "excess" blastocysts from IVF clinics	• can produce all cell types • relatively easy to identify, isolate, maintain, and grow in the laboratory • stem cells may be genetically matched to patient	• demonstrated success in some treatments • stem cells may be genetically matched to patient
Limitations	• limited number of cell lines available for federally funded research • risk of creating teratomas (tumors) from implanting undifferentiated stem cells	• not yet achieved with human cells • risk of creating teratomas (tumors) from implanting undifferentiated stem cells	• produce limited number of cell types • not found in all tissues • difficult to identify, isolate, maintain, and grow in the laboratory
Ethical Concerns	• destruction of human blastocysts • donation of blastocysts requires informed consent	• destruction of human blastocysts • donation of eggs requires informed consent • concern about misapplication for reproductive cloning	• no major ethical concerns have been raised



Shinya Yamanaka studied genes that are important for stem cell function. When he transferred four such genes (1) into cells taken from the skin (2), they were reprogrammed into pluripotent stem cells (3) that could develop into all cell types of an adult mouse. He named these cells induced pluripotent stem (iPS) cells.



iPS cells can now be generated from humans, including patients with disease. Mature cells including nerve, heart and liver cells can be derived from these iPS cells, thereby allowing scientists to study disease mechanisms in new ways.

Mesencymal stem cells (MSCs) and DN

MSCs are adult multipotent stem cells that can differentiate into osteocytes, chondrocytes and adipocytes.

They are derived from many tissues including bone marrow, adipose tissue, nervous tissue, amniotic fluid, umbilical cord,placenta and dental pulps.

They express CD44,CD90, CD105 while do not express CD45, CD34

Front. Endocrinol., 06 June 2014 | doi: 10.3389/fendo.2014.00086

How can MSCs prevent or treat DN ?

CELL BIOCHEMISTRY & FUNCTION

CELL BIOCHEMISTRY AND FUNCTION
Cell Biochem Funct 2014; **32**: 453–463.
Published online 28 May 2014 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/cbf.3037

Bone-marrow mesenchymal stem cell transplantation to treat diabetic nephropathy in tree shrews

Xing-Hua Pan[1], Xiao-Yan Yang[1,2], Xiang Yao[1], Xiao-Mei Sun[3], Lu Zhu[1], Jin-Xiang Wang[1], Rong-Qing Pang[1], Xue-Min Cai[1], Jie-Jie Dai[3]* and Guang-Ping Ruan[1]*

[1]*Stem Cell Engineering Laboratory of Yunnan Province, Kunming General Hospital of Chengdu Military Command, Kunming, China*
[2]*Clinical College of Kunming General Hospital of Chengdu Military Command, Kunming Medical University, Kunming, China*
[3]*Yunnan Key Laboratory of Vaccine Research and Development on Severe Infectious Diseases, Center of Tree Shrew Germplasm Resources, Institute of Medical Biology, Chinese Academy of Medical Science and Peking Union Medical College, Kunming, China*

Diabetic nephropathy (DN) is a common microvascular complication of diabetes. We used a new DN model in tree shrews to validate the use of bone-marrow mesenchymal stem cell (BM-MSC) transplantation to treat DN. The DN tree shrew model was established by a high-sugar and high-fat diet and four injections of streptozotocin. 4',6-Diamidino-2-phenylindole labelled BM-MSCs were injected into tree shrews. The DN tree shrew model was successfully established. Blood glucose was significantly increased ($p < 0.01$) during the entire experiment. DN tree shrews showed dyslipidemia, insulin resistance and increased 24-h proteinuria. At 21 days after BM-MSC transplantation, glucose and levels of triglycerides, total cholesterol and 24-h urine volume were lower than in tree shrews with DN alone ($p < 0.01$) but were still higher than control values ($p < 0.01$). Levels of creatinine and urea nitrogen as well as 24-h proteinuria were lower for DN tree shrews with BM-MSCs transplantation than DN alone ($p < 0.05$). High-sugar and high-fat diet combined with STZ injection can induce a tree shrew model of DN. BM-MSCs injection can home to damaged kidneys and pancreas, for reduced 24-h proteinuria and improved insulin resistance.

ASBMT

Biology of Blood and Marrow Transplantation

Volume 14, Issue 6, June 2008, Pages 631–640

Biology

Systemic Administration of Multipotent Mesenchymal Stromal Cells Reverts Hyperglycemia and Prevents Nephropathy in Type 1 Diabetic Mice

Fernando E. Ezquer[1], Marcelo E. Ezquer[1, 2], Daniela B. Parrau[1], Daniel Carpio[1], Alejandro J. Yañez[3], Paulette A. Conget[1],

Can MSCs slow the progression of DN independent of glycemic control ?

ASBMT
Biology of Blood and Marrow Transplantation
Volume 15, Issue 11, November 2009, Pages 1354–1365

Biology

Endovenous Administration of Bone Marrow-Derived Multipotent Mesenchymal Stromal Cells Prevents Renal Failure in Diabetic Mice

Fernando Ezquer[1], Marcelo Ezquer[1,2], Valeska Simon[1], Fabian Pardo[3], Alejandro Yañez[3], Daniel Carpio[4], Paulette Conget[1]

Twenty-five to 40% of diabetic patients develop diabetic nephropathy, a clinical syndrome that comprises renal failure and increased risk of cardiovascular disease. It represents the major cause of chronic kidney disease and is associated with premature morbimortality of diabetic patients. Multipotent mesenchymal stromal cells (MSC) contribute to the regeneration of several organs, including acutely injured kidney. We sought to evaluate if MSC protect kidney function and structure when endovenously administered to mice with severe diabetes. A month after nonimmunologic diabetes induction by streptozotocin injection, C57BL/6 mice presented hyperglycemia, glycosuria, hypoinsulinemia, massive β-pancreatic islet destruction, low albuminuria, but not renal histopathologic changes (DM mice). At this stage, one group of animals received the vehicle (untreated) and other group received 2 doses of 0.5×10^6 MSC/each (MSC-treated). Untreated DM mice gradually increased urinary albumin excretion and 4 months after diabetes onset, they reached values 15 times higher than normal animals. In contrast, MSC-treated DM mice maintained basal levels of albuminuria. Untreated DM mice had marked glomerular and tubular histopathologic changes (sclerosis, mesangial expansion, tubular dilatation, proteins cylinders, podocytes lost). However, MSC-treated mice showed only slight tubular dilatation. Observed renoprotection was not associated with an improvement in endocrine pancreas function in this animal model, because MSC-treated DM mice remained hyperglycemic and hypoinsulinemic, and maintained few remnant β-pancreatic islets throughout the study period. To study MSC biodistribution, cells were isolated from isogenic mice that constitutively express GFP (MSC^{GFP}) and endovenously administered to DM mice. Although at very low levels, donor cells were found in kidney of DM mice 3 month after transplantation. Presented preclinical results support MSC administration as a cell therapy strategy to prevent chronic renal diseases secondary to diabetes.

TRANSPLANTATION
PROCEEDINGS

Delayed Treatment With Human Umbilical Cord Blood-Derived Stem Cells Attenuates Diabetic Renal Injury

J.H. Park, J. Park, S.H. Hwang, H. Han, H. Ha

Abstract

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease worldwide. Excess accumulation of extracellular matrix and the epithelial-to-mesenchymal transition contribute to renal fibrosis, which is associated with DKD. The present study examined whether delayed treatment with human umbilical cord blood–derived stem cells (hUCB-SC) showed a therapeutic effect on DKD progression. Experimental diabetes was induced by intraperitoneal injection of streptozotocin (STZ; 50 mg/kg) into 6-week-old male Sprague-Dawley rats. Age-matched control rats received an equivalent volume of sodium citrate buffer alone. At 4 weeks after the STZ injection when diabetic renal injury had developed, hUCB-SC were administered (1×10^6 cells/rat) through the tail vein. Four weeks after administering the hUCB-SC, rats were sacrificed and we measured indices of DKD, including urinary protein excretion as well as fibronectin, α-smooth muscle actin (α-SMA), and E-cadherin mRNA, and protein expression. Diabetic rats developed significantly increased urinary protein excretion and renal hypertrophy compared to those in control rats. Renal expression of fibronectin and α-SMA mRNA, and protein were increased significantly in diabetic rats compared to those in the controls. E-cadherin protein expression in diabetic kidneys decreased significantly. Intravenously administered hUCB-SC effectively reduced proteinuria, renal fibronectin, and α-SMA up-regulation, as well as renal E-cadherin down-regulation in diabetic rats without a significant effect on blood glucose. Engrafted hUCB-SC in diabetic kidneys were confirmed by human DNA PKcs. The results demonstrated that delayed treatment with hUCB-SC attenuated the progression of diabetic renal injury.

How can MSCs ameliorate glomerular injury ?

Inhibition of oxidative stress

DIABETES RESEARCH AND CLINICAL PRACTICE

Mesenchymal stem cells transplantation ameliorates glomerular injury in streptozotocin-induced diabetic nephropathy in rats via inhibiting oxidative stress

Shasha Lv, Jing Cheng, Aili Sun, Junhua Li, Weiwei Wang, Guangju Guan[1], Gang Liu[1], Moran Su

[1] These authors contributed equally to this work and should be considered co-corresponding authors.

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Anti-fibrotic effect

Diab Vasc Dis Res. 2014 May 19;11(4):251-261.

Mesenchymal stem cells ameliorate diabetic glomerular fibrosis in vivo and in vitro by inhibiting TGF-β signalling via secretion of bone morphogenetic protein 7.

Lv S[1], Liu G[1], Sun A[2], Wang J[3], Cheng J[1], Wang W[1], Liu X[1], Nie H[1], Guan G[4].

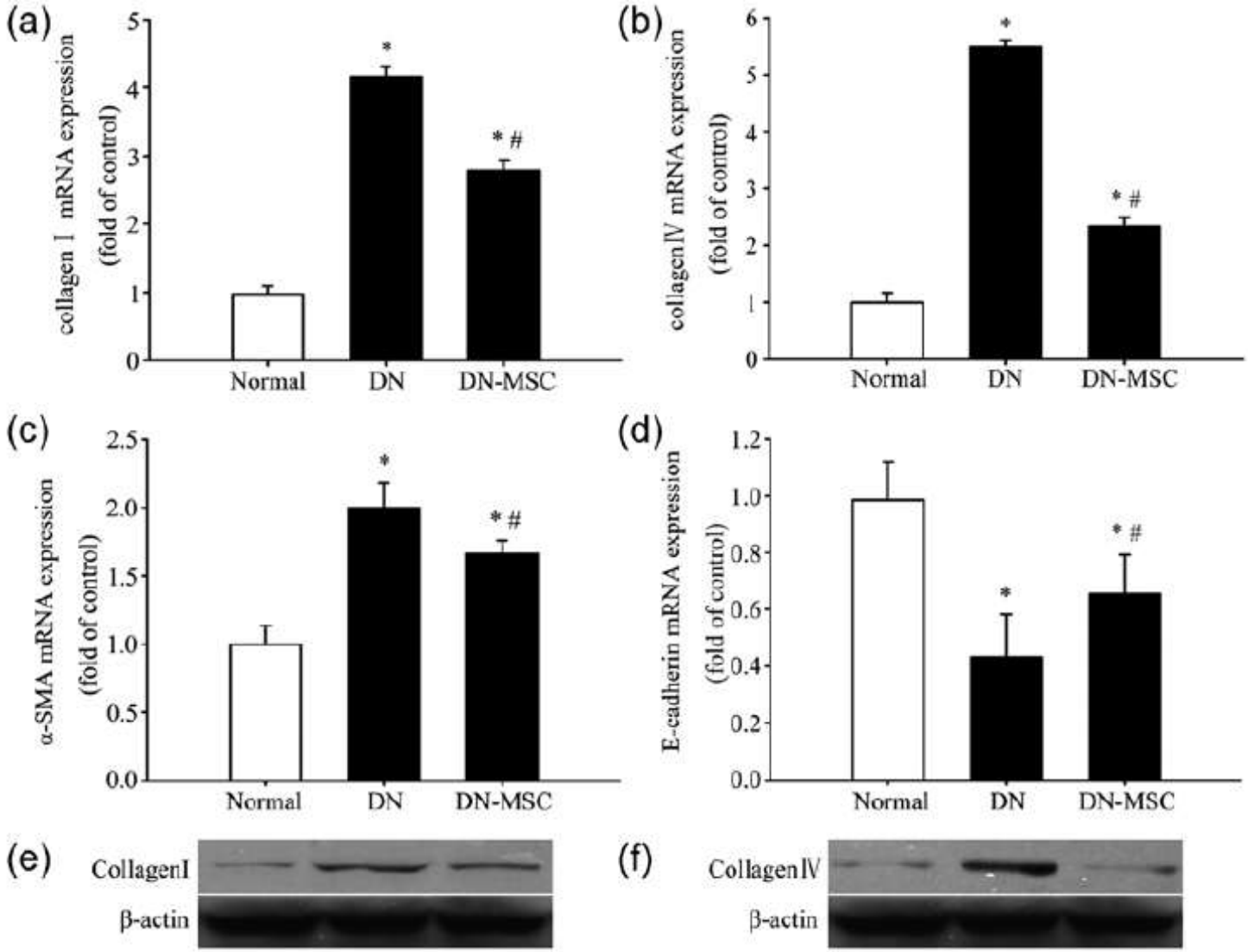
Abstract

Purpose: To investigate whether mesenchymal stem cells (MSCs) could inhibit transforming growth factor beta (TGF-β) signalling pathway by paracrine action.

Methods: Bone marrow–derived MSCs were transplanted to streptozotocin-induced diabetic rats via tail vein. MSC-conditioned media were used with a model of mesangial cell fibrosis induced by high glucose in vitro.

Results: At 8 weeks after MSC treatment, the renal function and the glomerulosclerosis as revealed by periodic acid Schiff stain was dramatically attenuated. The expression of collagen I, collagen IV and α-smooth muscle actin (SMA) in diabetic kidney was decreased, and E-cadherin increased after MSC treatment. The TGF-β signalling pathway was suppressed both in vivo and in vitro. MSCs secreted a significant amount of bone morphogenetic protein 7 (BMP7), in vitro, MSC-conditioned media inhibited TGF-β signalling stimulated by high glucose, and BMP7 neutralizing antibody blocked the inhibitory effect of MSC-conditioned media.

Conclusion: MSCs ameliorated glomerular fibrosis in vivo and in vitro by inhibiting TGF-β/Smad signalling pathway via secretion of BMP7.



Diab Vasc Dis Res. 2014 May 19;11(4):251-261.

Amelioration of podocyte injury

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Stem Cell Res Ther. 2013; 4(5): 103.
Published online Sep 1, 2013. doi: 10.1186/scrt314

PMCID: PMC3856604

Mesenchymal stem cells protect podocytes from apoptosis induced by high glucose via secretion of epithelial growth factor

Diangeng Li,[#1] Nan Wang,[#1] Li Zhang,[1] Zhu Hanyu,[1] Bai Xueyuan,[1] Bo Fu,[1] Cui Shaoyuan,[1] Weiguang Zhang,[1] Sun Xuefeng,[1] Rongshan Li,[✉2] and Xiangmei Chen[✉1]

Results

hAd-MSC-CM reduced podocytic apoptosis in a dose-dependent manner, decreased the expression of podocytic cleaved caspase-3, and prevented the reduced expression and maintained the normal arrangement of podocytic synaptopodin and nephrin. However, human embryonic lung cell (Wi38)-CM failed to ameliorate podocytic apoptosis or injury. Twelve cytokines with concentration ratios (MSC-CM/Wi38-CM) >10-fold were identified. Epithelial growth factor (EGF) was singled out for its known ability to prevent apoptosis. Recombinant human EGF (rhEGF) prevented podocytic apoptosis and injury similarly to hAd-MSC-CM but, upon blockade of EGF, the beneficial effect of hAd-MSC-CM decreased dramatically.

ASBMT
Biology of Blood and Marrow Transplantation
Volume 19, Issue 4, April 2013, Pages 538–546

Mesenchymal Stem Cells Ameliorate Podocyte Injury and Proteinuria in a Type 1 Diabetic Nephropathy Rat Model

Shuai Wang[1,2], Yi Li[1], Jinghong Zhao[1], Jingbo Zhang[1], Yunjian Huang[1],

Abstract

Mesenchymal stem cells (MSC) attenuate albuminuria and preserve normal renal histology in diabetic mice. However, the effects of MSC on glomerular podocyte injury remain uncertain. The aim of this study was to evaluate the effects of MSC on podocyte injury in streptozotocin (STZ)-induced diabetic rats. Thirty days after diabetes induction by STZ injection (65 mg/kg, intraperitoneally) in Sprague-Dawley rats, the diabetic rats received medium or 2×10^6 enhanced green fluorescent protein-labeled MSC via the renal artery. In vivo tracking of MSC was followed by immunofluorescence analysis. Diabetes-related physical and biochemical parameters were measured on day 60 after the MSC infusion. The expression of podocyte markers (nephrin and podocin), podocyte survival factors (VEGF and BMP-7), and the ultrastructural pathology of podocytes were also assessed. MSC were only detected in the glomeruli from the left kidney receiving MSC infusion. Compared with medium-treated diabetic rats, rats treated with MSC showed a suppressed increase in kidney weight, kidney to body weight index, creatinine clearance rate, and urinary albumin to creatinine ratio; however, the treatment had no effect on blood glucose or body weight levels. Furthermore, the MSC treatment reduced the loss of podocytes, effacement of foot processes, widening of foot processes, thickening of glomerular basal membrane (GBM), and loss of glomerular nephrin and podocin. Most important, MSC-injected kidneys expressed higher levels of BMP-7 but not of VEGF. Our results clearly demonstrated that intra-arterial administration of MSC prevented the development of albuminuria as well as any damage to or loss of podocytes, though there was no improvement in blood sugar levels. The protective effects of MSC may be mediated in part by increasing BMP-7 secretion.

Anti-inflammatory

International Immunopharmacology

Volume 17, Issue 2, October 2013, Pages 275–282

Mesenchymal stem cells transplantation ameliorates glomerular injury in streptozotocin-induced diabetic nephropathy in rats via inhibiting macrophage infiltration

Sha-Sha Lv[a], Gang Liu[a, 1], Jian-Ping Wang[b], Wei-Wei Wang[a], Jing Cheng[a], Ai-Li Sun[c], Hai-Ying Liu[a], Hui-Bin Nie[a], Mo-Ran Su[d], Guang-Ju Guan[a, 1]

Our study suggest that MSCs treatment ameliorates DN via inhibition of MCP-1 expression by secreting HGF, thus reducing macrophages infiltration, down-regulating IL-1β, IL-6, TNFα expression in renal tissue in diabetic rats.

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DIABETOLOGY & METABOLIC SYNDROME

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Diabetol Metab Syndr. 2014; 6: 34.
Published online Mar 9, 2014. doi: 10.1186/1758-5996-6-34

PMCID: PMC4007638

The role of bone marrow derived-mesenchymal stem cells in attenuation of kidney function in rats with diabetic nephropathy

Mohamed Talaat Abdel Aziz,[1] Mohamed Abdel Aziz Wassef,[1] Hanan Hosni Ahmed,[1] Laila Rashed,[1] Soheir Mahfouz,[2] Mayssa Ibrahim Aly,[3] Rania Elsayed Hussein,[1] and Mai Abdelaziz[1]

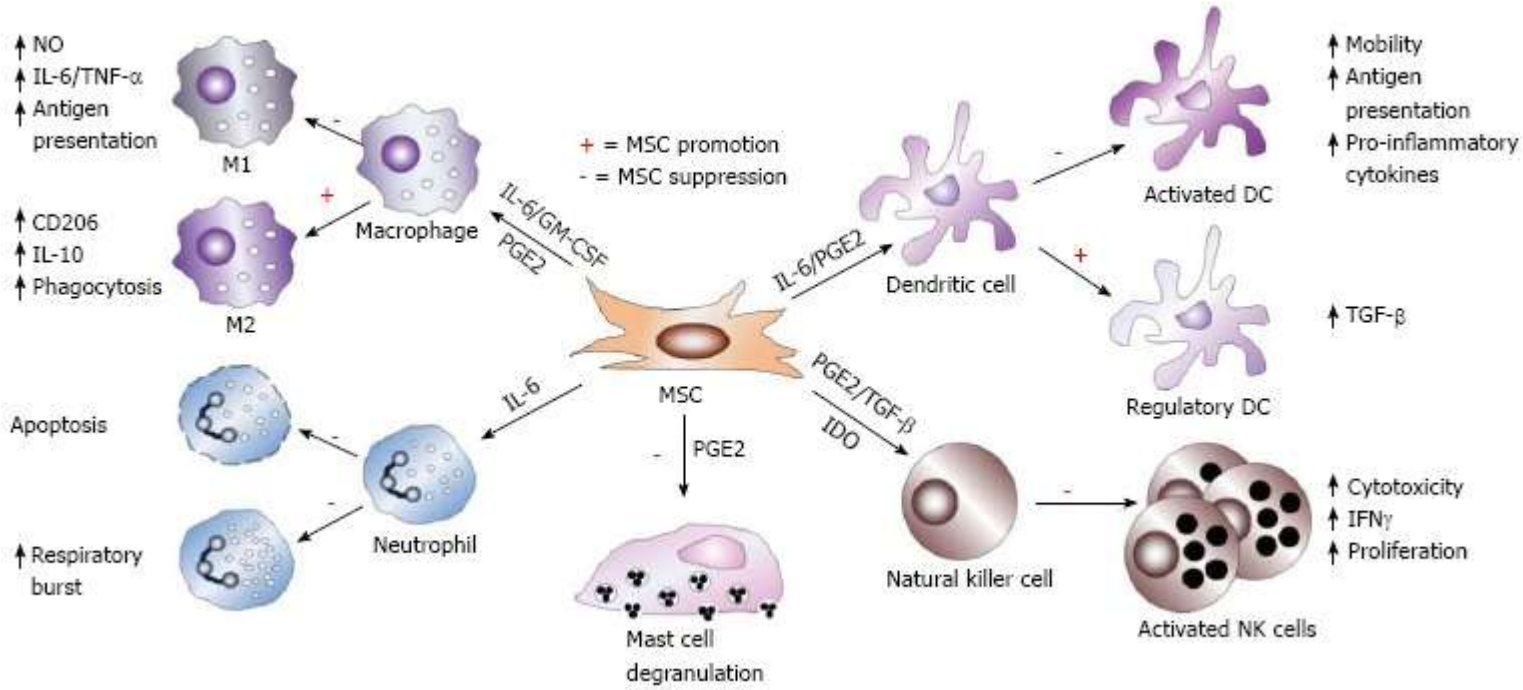
Results

MSC therapy significantly improved 24 h urinary albumin, serum urea and creatinine concentrations, increased angiogenic growth factor VEGF, and anti-apoptotic protein bcl2 while decreased the pro-inflammatory TNF-α, fibrogenic growth factor TGF β, and pro-apoptotic protein Bax. The histopathology examination showed patchy areas of minimal necrosis and degeneration in renal tubules.

Immunomodulatory effect

World Journal of Stem Cells

World J Stem Cells. Nov 26, 2014; 6(5): 526–539.
Published online Nov 26, 2014. doi: 10.4252/wjsc.v6.i5.526



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World J Stem Cells. Nov 26, 2014; 6(5): 526–539.
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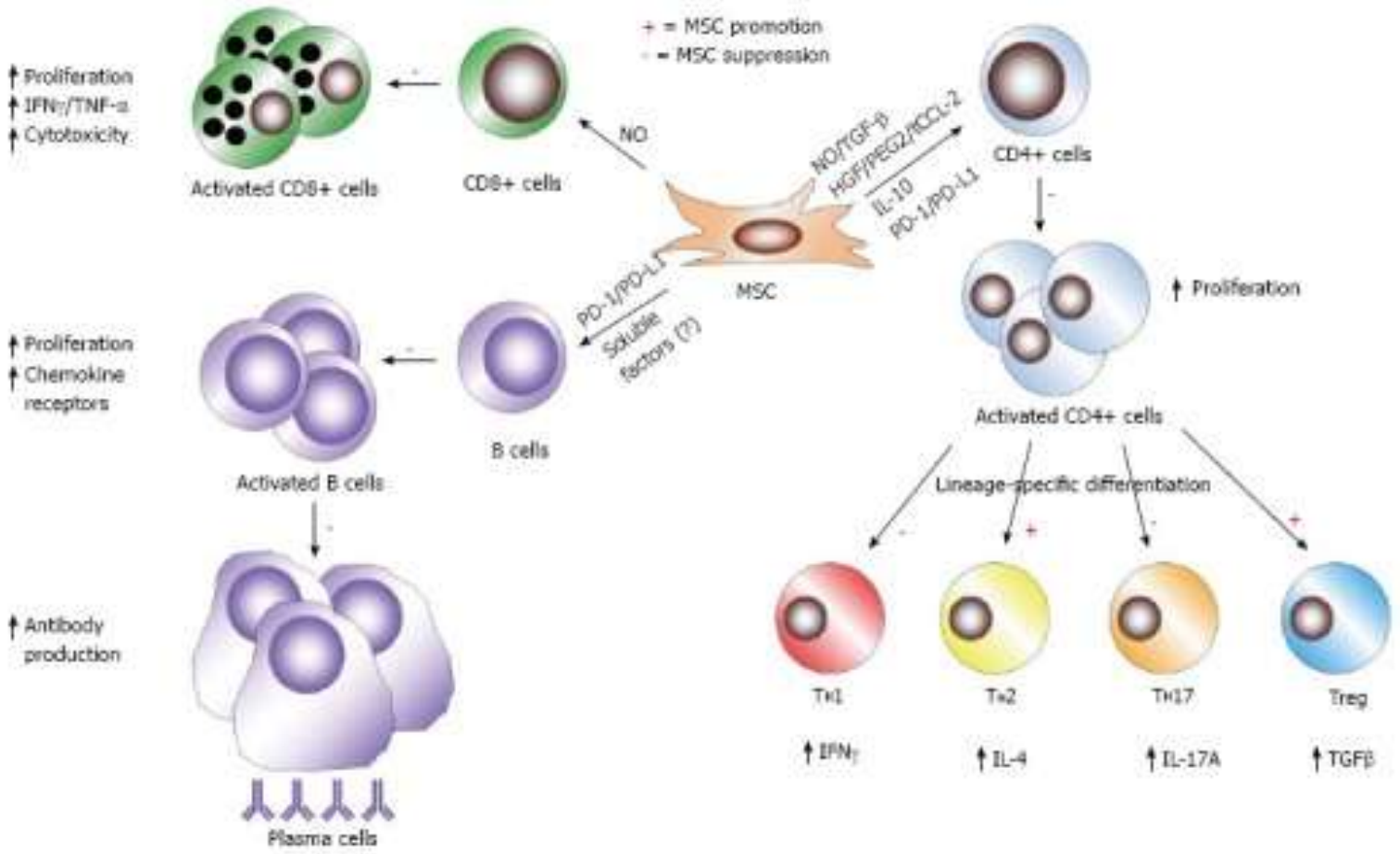


Can MSCs ameliorate glomerular injury by direct differentiation and regeneration of damaged cells ?

Potential limitations to clinical application

- Poor engraftment and limited differentiation under in vivo conditions
- The potential of MSCs to differentiate into unwanted mesenchymal lineages
- Possible malignant transformation and cytogenic aberrations

Concise Review: Mesenchymal Stem Cell Treatment of the Complications of Diabetes Mellitus
Stem Cells. Jan 2011; 29(1): 5–10.

Any clinical trials ?

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

There are currently **747** open studies of MSC safety and efficacy in the treatment of human diseases.

In relation to DM, there are currently **49** open clinical trials using MSCs to treat T1DM, T2DM, or their associated complications.

Only **one** clinical trial on DN.

Safety and Efficacy of Mesenchymal Precursor Cells in Diabetic Nephropathy

This study is ongoing, but not recruiting participants.

Sponsor:
Mesoblast, Ltd.

Information provided by (Responsible Party):
Mesoblast, Ltd.

ClinicalTrials.gov Identifier:
NCT01843387

First received: April 23, 2013
Last updated: August 13, 2014
Last verified: August 2014
History of Changes

Estimated Enrollment:	30
Study Start Date:	July 2013
Estimated Study Completion Date:	September 2015
Estimated Primary Completion Date:	September 2014 (Final data collection date for primary outcome measure)

IRCT
Iranian Registry of Clinical Trials

Investigation on autologous mesenchymal stem cell transplantation in diabetic nephrophaty (type one)

Project Overview

Millions of patients with diabetes mellitus in the EU are using prescription drugs to control their blood glucose levels. Poc control of blood glucose levels leads to a number of diabetic complications, including: nephropathy, retinopathy, cardiomyopathy, neuropathy, impaired bone repair and wound ulceration. At present, there are few therapeutic options available to control initiation and progression of diabetic complications and they continue to present challenging disease management issues for clinicians. The REDDSTAR Project will comprehensively examine if Stromal Stem Cells can safely control glycaemia and alleviate damage caused by six diabetic complications.

What about in vitro differentiation of MSCs to functioning nephron cells?

Cell Biol Int. 2014 Apr;38(4):497-501. doi: 10.1002/cbin.10231. Epub 2014 Jan 10.

In vitro differentiation of mesenchymal stem cells into mesangial cells when co-cultured with injured mesangial cells.

Wong CY[1], Tan EL, Cheong SK.

Author information

Abstract

Mesangial cells are one of the three major cell types of the kidney glomerulus that provide physical support for the glomerular capillary lumen of the kidney. Loss of **mesangial cells** due to pathologic conditions, such as glomerulonephritis and diabetic nephropathy, can impair renal function. Mesenchymal stem **cells** (MSC) are attractive candidates for kidney repair therapy since they can enhance recovery and protect against kidney failure. MSC can differentiate into **mesangial cells** in vivo. We have investigated the ability of MSC to differentiate into **mesangial cells** in vitro; they were co-cultured with oxidant-injured **mesangial cells** before being analysed by flow cytometry and for contractility. MSC co-cultured with injured **mesangial cells** had a **mesangial** cell-like morphology and contracted in response to angiotensin II. They expressed CD54(-) CD62E(+) in direct contrast to the CD54(+) CD62E(-) of pure MSC. In conclusion, MSC can differentiate into **mesangial cells** in vitro when co-cultured with injured **mesangial cells**.

Single Adult Kidney Stem/Progenitor Cells Reconstitute 3-Dimensional Nephron Structures *in Vitro*

1. Shinji Kitamura[1,*],
2. Hiroyuki Sakurai[2] and
3. Hirofumi Makino[1]

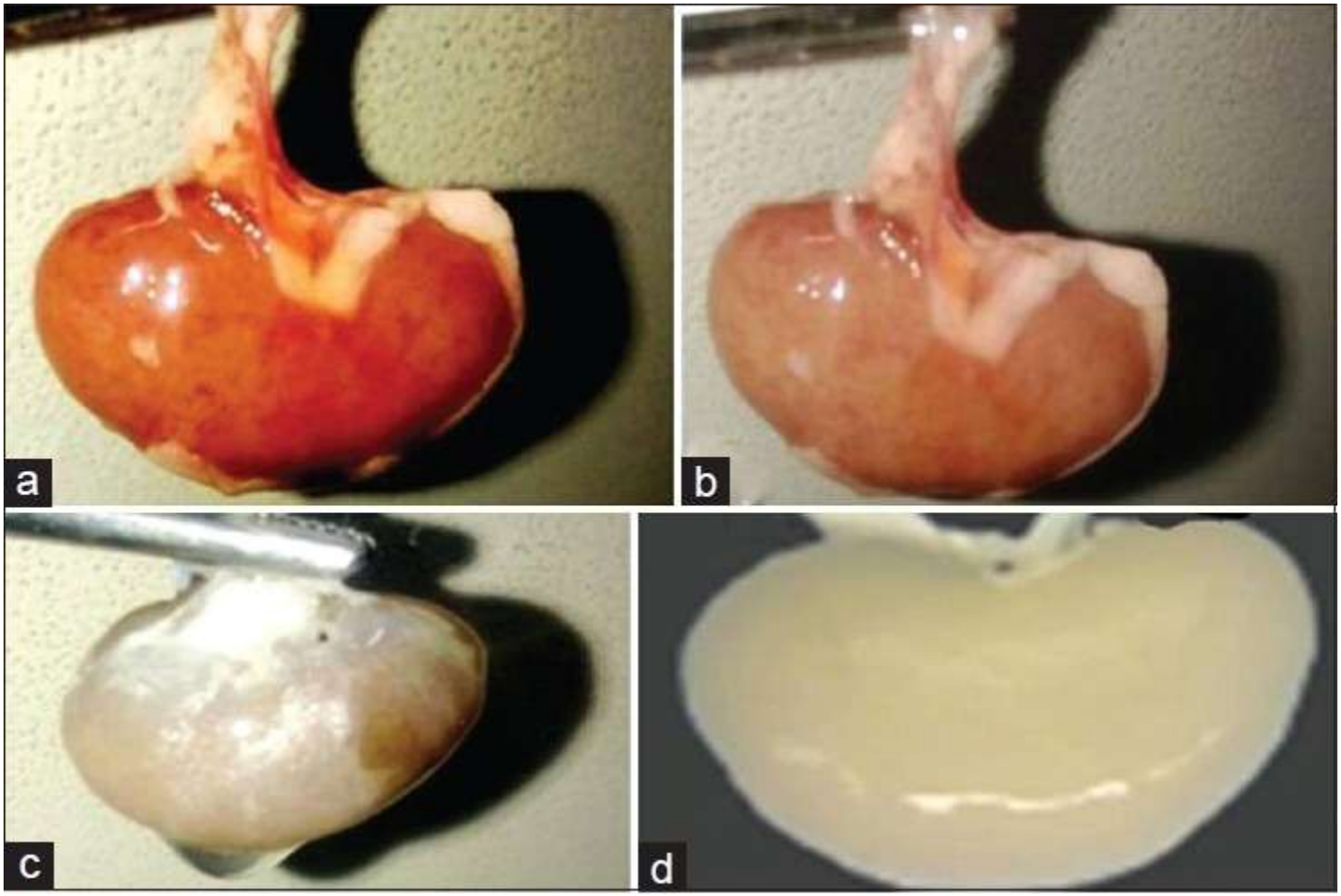
DOI: 10.1002/stem.1891

STEM CELLS®

AlphaMed Press

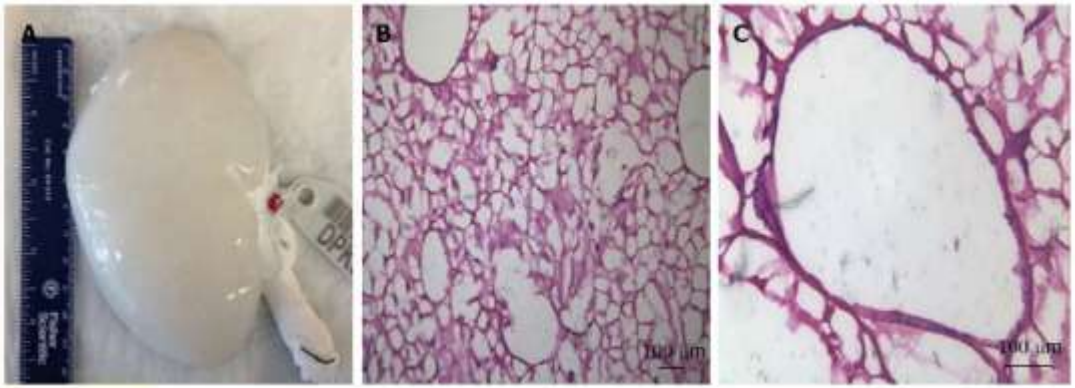
Here, we show that adult kidney stem/progenitor cells (KS cells), derived from the S3 segment of adult rat kidney nephrons, can reconstitute a 3-dimensional kidney-like structure *in vitro*. Kidney-like structures were formed when a cluster of KS cells was suspended in an extracellular matrix gel and cultured in the presence of several growth factors. Morphological analyses revealed that these kidney-like structures contained every substructure of the kidney, including glomeruli, proximal tubules, the loop of Henle, distal tubules and collecting ducts, but no vasculature. Our results demonstrate that a cluster of tissue stem/progenitor cells has the ability to reconstitute the minimum unit of its organ of origin by differentiating into specialised cells in the correct location. This process differs from embryonic kidney development, which requires the mutual induction of two different populations of progenitors, metanephric mesenchymal cells and ureteric bud cells.

Whole kidney regeneration



Preparation of natural three-dimensional goat kidney scaffold for the development of bioartificial organ

Indian J Nephrol. 2014 Nov-Dec; 24(6): 372–375.



A decellularized pig kidney scaffold and its extra cellular matrix after decellularization. A: Decellularized pig kidney scaffold; B: Hematoxylin and eosin staining of the decellularized pig kidney scaffold shows a decellularized extracellular matrix (× 200); C: Hematoxylin and eosin staining of the decellularized pig kidney scaffold shows a decellularized extracellular matrix (× 400). Permission of Wake Forest Institute for Regenerative Medicine.

World J Nephrol. Aug 6, 2014; 3(3): 24–30.

Tissue Eng Part A. 2014 May;20(9-10):1486-98. doi: 10.1089/ten.TEA.2013.0269. Epub 2014 Jan 29.

Recellularization of well-preserved acellular kidney scaffold using embryonic stem cells.

Bonandrini B[1], Figliuzzi M, Papadimou E, Morigi M, Perico N, Casiraghi F, Dipl C, Sangalli F, Conti S, Benigni A, Remuzzi A, Remuzzi G.

Author information

Abstract

For chronic **kidney** diseases, there is little chance that the vast majority of world's population will have access to renal replacement therapy with dialysis or transplantation. Tissue engineering would help to address this shortcoming by **regeneration** of damaged **kidney** using naturally occurring scaffolds seeded with precursor renal cells. The aims of the present study were to optimize the production of three-dimensional (3D) rat **whole-kidney** scaffolds by shortening the duration of organ decellularization process using detergents that avoid nonionic compounds, to investigate integrity of extracellular matrix (ECM) structure and to enhance the efficacy of scaffold cellularization using physiological perfusion method. Intact rat kidneys were successfully decellularized after 17 h perfusion with sodium dodecyl sulfate. The **whole-kidney** scaffolds preserved the 3D architecture of blood vessels, glomeruli, and tubuli as shown by transmission and scanning electron microscopy. Micro-computerized tomography (micro-CT) scan confirmed integrity, patency, and connection of the vascular network. Collagen IV, laminin, and fibronectin staining of decellularized scaffolds were similar to those of native **kidney** tissues. After infusion of **whole-kidney** scaffolds with murine embryonic stem (mES) cells through the renal artery, and pressure-controlled perfusion with recirculating cell medium for 24 and 72 h, seeded cells were almost completely retained into the organ and uniformly distributed in the vascular network and glomerular capillaries without major signs of apoptosis. Occasionally, mES cells reached peritubular capillary and tubular compartment. We observed the loss of cell pluripotency and the start of differentiation toward meso-endodermal lineage. Our findings indicate that, with the proposed optimized protocol, rat kidneys can be efficiently decellularized to produce renal ECM scaffolds in a relatively short time, and rapid recellularization of vascular structures and glomeruli. This experimental setup may open the possibility to obtain differentiation of stem cells with long lasting in vitro perfusion.

CONCLUSION

- Pre-clinical studies show encouraging data regarding the use of MSCs in early stages of DN
- There is increased need for additional *in vitro* and *in vivo* studies to fully describe in detail the mechanisms of MSC-mediated cell therapy
- Pre-clinical and clinical studies are needed to evaluate safety and confirm efficacy of MSCs.
- Though a functional bioengineered kidney is still a big challenge, this field may give hope to patients with ESKD including those with DN.

THANK YOU